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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,666	04/06/2001	Timothy J. Neuberger	365279-001	6738

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/827,666	NEUBERGER ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2005*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12,19-31,34-51,55-74* is/are pending in the application.

4a) Of the above claim(s) *29-31,37-45 and 59-66* is/are withdrawn from consideration.

5)☐ Claim(s) *73, 74* is/are allowed.

6)☒ Claim(s) *8-12,19-28,34-36,46-51,55-58 and 67-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, with traverse, with the Group III is acknowledged. Applicants traverse the restriction requirement on the grounds that there would be no burden in searching the entire groups. This argument is not persuasive, as claimed invention would be distinctive, each from the other for the reason of the record. Furthermore, the search of the entire groups in the non-patent literature (a significant part of a thorough examination) would be burdensome. Therefore, the requirement is still deemed proper, and made Final. Claims 8-11, 19-21, 24, 27, 34-36, 55-58 and 67-72 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

Status of Application

2. By Amendment filed July 10, 2006, claims 8, 19, 21, 24, 27, 34-36, 46-47, 50-51, 55 and 57 have been amended and claims 12, 22-23, 25-26, 28 and 48 have bee cancelled.

3. Claims 46-47, 49-51 and 73-74 are currently pending for prosecution on the merit.

4. Applicant's amendment filed July 10, 2006 requiring "an injury to nervous system tissue in a mammal...", "nervous system tissue is the result of a contusion injury..." and "nervous system tissue is caused by surgery" necessitates a new ground of rejection(s) in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 46-47, 49-51 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "treating spinal cord injury by administering bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated animal to a site of injury in animal", does not reasonably provide enablement for "treating injury to nervous system tissue" with the administration of neural stem cells or neural precursor cells obtained from a first mammal treated with compounds of formula (II). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the quantity of experimentation necessary; the amount of direction or guidance presented; the presence or absence of working examples; the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; and the breadth of the claims When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The amended claims relate to a method for treating injury to nervous system tissue in a mammal (claims 46-51), particularly spinal cord injury (claims 73-74), by administering neural stem cells, neural precursor cells or progenitor cells obtained from a first mammal treated with compounds of formula (II) to a site having a nervous system injury in the first mammal or to a site having a nervous system injury in a second mammal.

The interpretation of the instant claims (particularly independent claim 46) allow for the inclusion of injury to spinal cord, brain, cerebral cortex, cerebellar cortex, the meninges (connective coverings of the brain), glial cells, choroids plexus and etc... The scope of the instant invention is very broad encompassing the treatment of complex neurodegenerative conditions (e.g., multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, diabetes, senile dementia, dysplasia, myelitis, spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, mitochondrial multi.system disorder, transverse myelitis, anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy, Down's Syndrome in middle age, Diffuse Lewy body disease, Wernicke-Korsakoff syndrome, chronic alcoholism; Creutzfeldt-Jakob disease, Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease, Dementia pugilistica, etc...), that are known today, and those that may be discovered in the future.

The instant specification discloses that the instant invention relates to promoting neural tissue regeneration or neural expression. The specification defines neural tissue as "all tissue endogenous to the nervous system" (page 13, lines 10-12 and lines 22-26); neural expression as the expression of any proteins indicative of neural tissue growth or neural tissue cell differentiation from progenitor cells (page 13, lines 13-18); and neural progenitor cells as "any cell that can differentiate into a neural tissue cell, or be induced to differentiate into a neural tissue cell, including neural precursor cells, whether directly or through intermediate cell stages" (page 14, lines 1-3). As the specific embodiments of the invention, the instant specification discloses in-vitro study testing the activity of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide

in increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF and NF-PO4 (Examples 1 and 2) and in-vitro study testing the activity of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide in increasing the growth of neurons or astrocytes (Example 4). The instant specification also discloses that animals (Fischer F344 female rats) treated with bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated donor animal (rat) demonstrates a decrease in cavity size at the contusion injury site, in vivo or ex vivo study (Example 3).

The prior art recognizes the treatment of spinal cord injury by replacing damaged neural tissue with transformed cells of neural and non-neural origins, neutralizing the nerve-growth inhibitory properties of various proteins in the CNS environment, as well as introduction of stem cells or progenitor cells in an animal model.

It is generally known in the art that the animal model (spinal cord injury model) is poor analogue to human spinal cord injury since "human injury comes with its own set of physical, neurochemical, and histological pathologies that cannot be properly duplicated in a laboratory setting" ("Beyond Animal Research", Kristie Stoick, 2005, www.pcrm.org and "Gene Therapy for neurodegenerative diseases: fact or fiction?", Carter et al., 2001, British Journal of Psychiatry, 178, 392-394). Furthermore, it is recognized that "these animal models are invaluable, for each allows us to study one particular facet of cord injury, but definitely not the entire spectrum of spinal injuries" and the information derived from the animal model that is "fundamentally different from any human condition may be quantitative, reproducible, and statistically significant, but its relevance is limited to the artificial laboratory condition"

("Animal Models of Spinal Cord Injury", Stephen K Kaufman, M.D., Perspectives on Medical Research, Vol. 2, 1990).

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of injury to nervous system tissue or spinal cord injury prior to filling of the instant invention was an unpredictable art.

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single

embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575.

As stated above, with the exception of "treating spinal cord injury by administering bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated animal to a site of injury in animal", particularly rat, the skilled artisan cannot envision that (a) the administration of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide is capable of promoting regeneration of diverse nervous system tissues including neural cells, neural precursor cells, progenitor cells or tissue of neural origin (e.g., schwanne cells, stems cells, oligodendrites, etc...) in animals or human, furthermore the entire spectrum injury in nervous tissues including injury to spinal cord, brain, cerebral cortex, cerebellar cortex, the meninges (connective coverings of the brain), glial cells, choroids plexus and etc...

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the claimed utility of the instant compounds in human, furthermore for the treatment of "entire spectrum of nervous system tissue injury" encompassed by the instant claims. In the instant case, only a limited number of examples are set forth, thereby failing to provide sufficient working examples. Furthermore, the specification does not provide sufficient

guidance for the skilled artisan how to ascertain which neural tissues, neural precursor cells or progenitor cells other than bone marrow cells would be enabled in this invention in animals or human. Furthermore, the specification does not provide sufficient guidance for the skilled artisan how to ascertain that the growth of neuron or astrocytes by the administration of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide in vitro would lead to the improvement of the functional recovery of neurons, and provide the effective treatment of complex neurodegenerative diseases or conditions that may have unrelated manifestation in animal or human , without undue amount of experimentation.

For the reason given above, in view of the nature of the invention, the amount of guidance present in the specification, the breath of the claims, the relative skill of those in the art, and the predictability or unpredictability of the art, it would take undue trials and errors to practice the claimed invention.

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or

reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

Response to Arguments

6. Applicant's arguments filed July 10, 2006 have been fully considered but they are not persuasive.

Applicant's argument takes the position that based on the claim amendment filed July 10, 2006 and the support found particularly in Example 3 on pages 45-50 and also on page 28, lines 2-29; on page 30, lines 1-29 continuing on to page 21, lines 1-18, and Declaration signed by Dr. Timothy Neuberger filed November 5, 2004, it would not take undue experimentation for a skilled practitioner to practice the invention as currently claimed.

This argument is not found persuasive. As discussed in above, it is generally known in the art that the animal model (spinal cord injury model) is poor analogue to human spinal cord injury since "human injury comes with its own set of physical, neurochemical, and histological pathologies that cannot be properly duplicated in a laboratory setting" ("Beyond Animal Research", Kristie Stoick, 2005, www.pcrm.org and "Gene Therapy for neurodegenerative diseases: fact or fiction?", Carter et al., 2001, British Journal of Psychiatry, 178, 392-394). Furthermore, it is recognized that "these animal models are invaluable, for each allows us to study one particular facet of cord injury, but definitely not the entire spectrum of spinal injuries" and the information derived from the animal model that is "fundamentally different from any human condition may be quantitative, reproducible, and statistically significant, but its relevance

is limited to the artificial laboratory condition" ("Animal Models of Spinal Cord Injury", Stephen K Kaufman, M.D., Perspectives on Medical Research, Vol. 2, 1990).

As discussed above, in view of the nature of the invention, the amount of guidance present in the specification, the breath of the claims, the relative skill of those in the art, and the predictability or unpredictability of the art, the examiner maintains that it would take undue experimentation for one having ordinary skilled in the art to arrive at the claimed invention.

Conclusion

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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